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## Cholecystography

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**CHOLECYSTOGRAPHY**

**BY**

**RAYMOND G. DORNBERGER**

**SENIOR THESIS**

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## INTRODUCTION

In the preface of Graham and his associates' book, "Diseases of the Gall Bladder and Ducts", is the rather startling statement that between twenty and twenty-five per cent of all adults harbor gall stones and possibly an equal number suffer from cholecystitis without stones--or in other words, nearly one-half of the adult population is subject to disease of the biliary and hepatic systems. The clinical manifestations, however, do not correspond to this high incidence. Many are without symptoms and probably a greater number fall into the so-called functional gastrointestinal neuroses including "nervous indigestion" and "dyspepsia". Separation of the purely functional group whose chief complaint is indigestion from that group with early or late hepato-biliary disease is at best difficult and there is no degree of certainty as yet.

Prior to the advent of cholecystography, the roentgenologic evidence of cholelithiasis was very scant, and consisted chiefly in the visualization of opaque stones. Graham and Cole revolutionized the field of diagnosis in gall bladder disease with their monumental work on cholecystography in 1924. Since that time, cholecystography has been universally recognized as our most important agent in detecting gall bladder pathology. Cholecystography is relatively new and it involves an entirely new principle in roentgenology

since it is a test of functional capacity of a system. Techniques are still not standardized and the matter of interpretation is all important.

Therefore, since biliary disease is common, its differential diagnosis is difficult, and cholecystography offers our single greatest aid in this matter, the author has constructed this paper with the hope of gaining a better knowledge and understanding of this procedure. In addition to a discussion of the subject as a whole, there is included in this paper a report of a personal investigation of all cholecystographic studies made in the University of Nebraska Hospital over an eleven-year period.

## I DEFINITION

The discovery of a new method of roentgenological examination of the gall bladder was reported in 1924 by Graham and Cole (1). They demonstrated that when phenolphthalein, containing either iodine or bromine, was injected intravenously into animals or man, a sufficient concentration of the halogen was obtained in the gall bladder to cast a shadow on a film when exposed to the roentgen-ray. Graham and his associates applied the name "cholecystography" to the visualization of the gall bladder by this method, and the exposed roentgen-ray films were called "cholecystograms". (2)

## II HISTORY AND DEVELOPMENT

The demonstration of the striking effectiveness of the roentgenological visualization of the alimentary canal by the opaque meal in the diagnosis of gastric and intestinal conditions, and of the kidney pelves after the intraureteral injections of opaque substances led naturally to the desire to find some method by which other structures could be made to reveal abnormalities. Because of the very great frequency of affections of the biliary tract it was particularly desirable to have a method which would permit the visualization of the gall bladder. The story of the development of cholecystography is so fascinating that it will be told in detail.

Evarts A. Graham (3) was a surgeon who was particularly interested in chemistry--so much so that he decided to give up his small surgical practice and spent the years of 1913 and 1914 at the University of Chicago in the study of chemistry. The time so devoted was fruitful to the extent that it enabled him to think somewhat in chemical terms and thus to take advantage of the possibilities of the application of some relatively simple chemistry to the problem of the improved diagnosis of gall bladder disease. On several occasions Walter Mills and he conversed about the desirability of visualizing the gall bladder in some manner comparable to the visualization of the stomach and other parts of the alimentary canal. No satisfactory method, however, suggested itself until suddenly one evening, in the

winter of 1922, the idea occurred to him that since Abel and Rowntree (4) had demonstrated the fact that the chlorinated phenolphthaleins were excreted almost entirely through the bile it might be possible, by substituting for the chlorine atoms other atoms which would be opaque to the x-ray, to obtain a shadow of the gall bladder.

From the Eastman Kodak Company he obtained some of the free acid of tetraiodophenolphthalein already prepared since they had such a substance advertised in their list of indicators. After receiving the material he turned it over to Warren Cole, in July, 1923, and asked him to inject it into some animals to see if he could visualize their gall bladders with it. Before injecting the material into dogs they converted it into the sodium salt because the free acid was naturally less soluble than the sodium salt. Six dogs were injected intravenously, and x-ray photographs were made of the gall bladder regions in all of them at frequent intervals after the injection. In five of the dogs no shadow was obtained, but fortunately a faint shadow was obtained in the sixth one. At first they were at a loss to understand why they had obtained a faint shadow in one dog but none at all in the other five animals. The idea then occurred to them that the reason for the failure was probably due to the fact that the animals were not fasting and that, therefore, the injected substance was not staying in the gall bladder for a long enough time to be concentrated and, therefore, to make a shadow. Upon investigating the matter they found that by acci-



dent or through some mishap or other the animal keeper had neglected to feed the one dog on the morning of the experiment but he had fed all the others.

With the clue that the failure to cast a shadow was due to the presence of food in the stomach and duodenum it was then a relatively simple matter to determine that shadows could be obtained in almost every instance during a fasting period. At about this time Glover H. Copher was added to the group conducting the investigation. The matter of dosage and toxicity had to be settled because several of the animals died. They turned hopefully to the bromine homologue. After considerable experimenting with various dyes, the Mallinckrodt Chemical Works supplied them with an exceptionally pure product of the sodium salt of tetrabromphenolphthalein. With this dye they obtained good shadows of the gall bladder with much less toxic effects, in spite of the larger dose required.

Up to that time their only idea in visualizing the gall bladder had been to introduce something into it which would visualize any contained stones or deformities of the organ. A colored woman in the Barnes Hospital who presented a very characteristic clinical picture of gallstones seemed to present satisfactory conditions for the first trial in the human. They all had hopes that a sharp image of gallstones in the woman's gall bladder would be demonstrated. An ordinary x-ray film before the injection of the dye had failed to show any stones.

To their great disappointment and consternation the patient showed no shadow at all of her gall bladder after injection, in spite of a series of films which were made. Their disappointment was made more intense by the fact that Graham operated this patient and found a gall bladder which contained many stones of different sizes. It seemed then, for the moment as if their high hopes of improving the diagnosis of gall bladder disease had been dashed to the ground. Soon, however, the idea occurred to them that since they had been obtaining excellent shadows in their experimental animals, which presumably had normal gall bladders, the reason for their failure to produce a shadow in the markedly diseased gall bladder might be because the diseased gall bladder could not properly concentrate the material which was brought to it. They also took into consideration the possibility that there might have been an obstruction of the cystic duct which prevented the entrance of the material into the organ, but in the case in which they had had a failure Graham had found an abundance of bile in the gall bladder at operation with no evidence of obstruction. They were, therefore, forced to believe that a diseased wall in itself might be sufficient to result in non-visualization because of the failure of concentration.

This conclusion led them to the next step which was to inject some patients who supposedly had normal gall bladders. They obtained well visualized shadows. This result, while

gratifying, made it necessary to change their whole conception of the possible applicability of such a test to the patient. For instead of having a method which would with certainty reveal gallstones in the x-ray picture they found that they were, on the contrary, dealing with a method which was more of a functional test of the gall bladder and one which would show the gall bladder most plainly under normal conditions, and not at all in those conditions in which the organ was very badly diseased no matter whether stones were present or not.

The big disadvantage at first was that in patients in whom the best shadows were obtained sometimes severe reactions occurred. A search was then made for a better dye. In all they tried some forty-eight different substances, of which thirteen were shown to visualize the gall bladder. Most of these thirteen substances had disadvantages of one kind or another. Whitaker and Milliken (5), who were working independently of Graham and his associates, were fortunate enough to secure good samples of tetraiodophenolphthalein and they reported in January, 1925, a comparative study of the two dyes. They demonstrated that approximately one-half as much of sodium tetraiodophenolphthalein need be used as the bromine salt, and the smaller dose was less toxic. This was soon confirmed by Graham and Cole (6) (7). About a year later, Graham and his associates (8) reported on the use of the isomer of this sub-

stance, namely, sodium phenoltetraiodophthalein as the most suitable of the available dyes for intravenous injection. It is interesting to note that the first substance Graham and Cole used was tetraiodophenolphthalein which is still the dye of choice in cholecystography and it was only because of the toxic impurities in the initial product that it was ever abandoned. (2)

### III PRINCIPLE

From the radiological standpoint the problem of visualizing the gall bladder differs in nearly every respect from that demanded for the development of any of the other artificial contrasts. It embodies an entirely new and original radiological principle, namely, the utilization of the specific functions of a system to engender a difference in density. Therefore, cholecystography is largely a test of physiological capacity in contradistinction to the almost wholly mechanistic nature of the opaque meal examination, pyelography, and the like.

From a physiological standpoint then, the dye is administered either by mouth or intravenous injection. It is taken up by the blood stream, excreted in the bile by the liver, and diverted into the gall bladder by the action of the sphincter of the common duct, if the subject is fasting. Within the gall bladder, the bile and iodine become more concentrated, due to absorption of water by the wall of the viscus. The ability of the gall bladder to concentrate its contained bile, as shown by Rous and McMaster (9), indicates that a sufficient time must elapse before a shadow of maximal density occurs. It is during this period of about twenty-four hours that shadows may be procured on films by exposing the gall bladder to roentgen-rays. The iodine is removed from the normal gall bladder as it empties, and with it goes the opacity of the

organ to the roentgen-ray. By this means, the roentgenologist can study the size, shape and position, but more especially the filling, the concentrating function, and the emptying of the gall bladder. Reasoning from these premises, the conclusion would have to be drawn that the shadows of sharpest contrast would be obtained in normal individuals. Similarly, also no shadow would be expected to appear if the liver were unable to excrete the substance in sufficient amount, if the cystic duct were occluded, or if the function of the gall bladder were sufficiently impaired to prevent the concentration of the material. Intermediate degrees of changes from the normal conditions will result in the appearance of shadows which require expert interpretation. It is because of its sensitiveness to slight functional changes that cholecystography becomes of great value in the diagnosis of the cases of early and comparatively mild cholecystitis which are the most difficult to diagnose by any other method, either clinical or laboratory. Prior to the advent of cholecystography most cases could be accurately diagnosed only after they had gone to the stage of advanced pathology. By means of this test of function, its originators were anticipating another phase in preventive medicine by the possibility of early accurate diagnosis in gall bladder disease inasmuch as early operative treatment would prevent most of the ravages of long standing cholecystitis with its accompanying serious effects on the liver and pancreas. (2) (10)

#### IV ADMINISTRATION AND TECHNIQUE

##### A. Intravenous Method

There have been countless discussions devoted to the relative merits of the intravenous and oral methods. Graham and his associates (11) (6) (7) (8) (1) including Sherwood Moore (12) used the intravenous method from the first. Their conception was that cholecystography was a measure of functional capacity of the gall bladder and for that reason they held that for the sake of accuracy in making the test, the intravenous injection was the method of choice. As previously cited (8), they discovered that sodium phenoltetraiodophthalein, the isomer of sodium tetraiodophenophthalein, gave more satisfactory results in the intravenous work. Intravenous administration made it certain that a full dose had been introduced into the circulation and excluded any question of absorption. In 1927, Graham (13) summarized the results of some fifteen different groups of workers as to accuracy in diagnosis. The percentage of correctness in three hundred eighty cases of all authors using intravenous method was ninety-five while the percentage of correctness in one hundred eighty-one cases of all authors by the oral method was eighty-nine--another point in favor of the intravenous route.

Zink (14), in 1926, reported the use of intravenous dye in five hundred thirteen cases and preferred this method to the oral except when contra-indicated by any one of the

following:

1. Common duct obstruction
2. Extensive hepatic destruction
3. Hypertension
4. Cardiac disease
5. Hyperthyroidism

He used the oral method in one hundred thirty-one cases and stated that cholecystograms made by that method were reliable only in cases presenting

1. Normal shadow
2. Presence of stones
3. Topographical defects (pericholecystitis)

Boardman (15) reached a similar conclusion in the study of twenty-five cases examined by both oral and intravenous methods. There was agreement in nine, or thirty-six per cent, and disagreement in sixteen, or sixty-four per cent. In every case of disagreement the intravenous method gave evidence of a more normally functioning biliary system. He emphasized the fact that after oral administration only the evidence of a perfectly normally functioning tract was to be accepted.

Verbrycke (16) was one of the ardent proponents of the intravenous technique from the onset. Soon after Graham and Cole's first report he began using the test and in 1927 reported his preference for this method stating that toxic



reactions were the exception in his group of patients. He concluded that in his estimation cholecystographic diagnosis was probably twenty per cent more accurate than clinical diagnosis and at least ten per cent more accurate than exploratory diagnosis.

Another of the early intravenous enthusiasts was Case (17) (18) (19) (20), who found that method gave a maximum amount of information in comparison with the oral, jejunal, and rectal methods. He concluded that the absence of the gall bladder shadow was worth at least ninety-five per cent toward indicating operation, a normal Graham test should deter the surgeon from operating except in the face of the clearest clinical evidence of gall bladder disease, and finally that impaired function by the intravenous method had great significance and should be interpreted as disease while such could not be said for oral administration.

Waters and Firor (21) summarized the advantages of intravenous cholecystography quite adequately in 1930. First they considered the complications---

1. Urticaria. This was the commonest and least serious--promptly controlled by five to ten minims of adrenalin hydrochloride given hypodermically.
2. "Sore arm". This they considered a cellulitis due to the action of the dye in the subcutaneous

tissues and was the fault of the person who made the injection. They recommended the isomeric salt, phenoltetraiodophthalein because it was less irritating.

3. Endophlebitis obliterans. They considered the commonly used term "venous thrombosis" as incorrect and pointed out that in reality the condition was not a thrombosis but an inflammation of the intima resulting in obliteration of the lumen of the vein. Digital pressure upon the vein during or immediately following the injection was conducive to intimal adherence just as in the surgical treatment of varicose veins by injection.

Only two conditions contraindicated the use of the intravenous method, namely, cardiac decompensation and threatened uremia. As regards diagnostic accuracy of the oral method in the operative group of cases, they called attention to the fact that this group usually presented outspoken clinical indications for surgical intervention. In two years' experience with intravenous cholecystography, at least twenty-five per cent of those cases who had previously been grouped as normal by the oral method were, on the contrary, found pathological by the intravenous method. Finally, they emphasized the fact that the intravenous method insured a known amount of dye to be used and the procedure could be easily and safely carried out in office practice.

### B. Oral Method.

The first report of oral administration for production of cholecystograms was made by Menees and Robinson in February, 1925 (22). Their first work was done with sodium tetrabromphenolphthalein. Various types of containers were tried which would not dissolve in the stomach but would disintegrate in the intestine. Salol and keratin coated capsules were used but best results were obtained with formalin hardened gelatin capsules. Bicarbonate of soda was given with the dye to prevent precipitation by the hydrochloric acid of the stomach. The chief disadvantage of the oral method in their work was the nausea and vomiting and a certain number of patients were not able to retain the dye. Slight looseness of the bowels was observed in seven of thirty-seven cases. Thus, they thought the amount of dye absorbed would not be controlled.

Carman (23) noted catharsis after oral use of sodium tetrabromphenolphthalein, usually after enteric coated pills and less often following the use of plain gelatin capsules. Palefski (24) noted the alimentary reaction with sodium tetrabromphenolphthalein and gave morphine and atropine to counteract it. Whitaker, Milliken and Vogt (25), in forty-four instances of oral administration of the sodium tetraiodophenolphthalein noted vomiting five times, slight nausea seven times, and mild diarrhea in five cases. Using oral administration of

sodium tetraiodophenolphthalein, Larimore (26), in 1926, tried to associate the amount of free hydrochloric acid in the stomach with the alimentary disturbances. All of his patients sustaining reactions had an achlorhydria.

In 1925-26, Levyn and Aaron (27) compared the relative value of different coatings of capsules in regard to their dissolution in gastric and duodenal contents. Their results showed that even though the plain capsules digested readily, a large amount of a white acid form of tetraiodophenolphthalein was formed. This acid radical was insoluble in the duodenal contents. Therefore, they suggested the use of sodium bicarbonate to be given in combination capsules in order to do away with the insoluble acid radicals that were formed. This was accomplished by putting the dye in No. 3 plain capsules which were inserted in No. 0, the outer containing the sodium bicarbonate, and they proved superior to any other forms used, offering the highest percentage of visualized gall bladders. These men also experimented with strontium and sodium bromide as suggested by Sabatini and Milani (28) of Rome, who reported "remarkable results" in showing the gall bladder after ten to twenty grams had been given by mouth and fasting the patient over a long period of time. Though Levyn and Aaron closely followed the recommended technique, they were unable to obtain any vestige of a gall bladder shadow in twelve normal individuals. Graham, Cole, Copher

and Moore (2) were unable to produce satisfactory shadows of the gall bladder by using this method, although shadows were obtained. The patients also objected strenuously to the long fast and to the discomforts following such large doses of bromides. McCoy and Graham, R. S. (29), likewise did not find the method satisfactory.

In 1927, King and Martin (30) summarized their results in four hundred seven cases at Johns Hopkins. Tetraiodophenolphthalein was used in gelatin capsules and they recorded very satisfactory results but cautioned against normal functioning reports and cited an error of twenty per cent in the non-filling group.

Eusterman (31) summarized the cases at the Mayo Clinic up to 1927 and concluded that the intravenous method was more accurate, generally speaking, and in certain cases, especially after the oral administration, the test should be repeated by intravenous injection.

Stewart and Ryan (32) (33) were among the first and probably the most diligent of the early advocates of oral administration. Certainly they did much towards popularizing the oral method.

Until Fantus (34) came along in 1927, the simplicity of the oral method over the intravenous had been overbalanced by two disadvantages, namely, greater tendency toward reaction (especially nausea and vomiting) and lack of consistency in

absorption. He suggested giving the dye in a colloidal form to prevent nausea and vomiting, thus giving better absorption. Then Levyn and Aaron (35) found that the iodine dye could be given in liquid form by dissolving the dose in a small amount of distilled water and adding from 240 to 300 cc. of grape juice. Kirklin (36) in 1929, reported the use of 4 gms. of tetraiodophenolphthalein in simple fresh aqueous solution with grape juice added. This was taken after the evening meal which was fat free. In five hundred cases, nausea was seldom seen and flocculi of unabsorbed dye were seldom noted in the bowel.

Among the first men to combine the two methods of administration in an attempt to obtain greater efficiency in diagnosis were Sosman, Whitaker, and Edson (37). In 1925, these men reported their results by both methods preferring the intravenous method and suggested confirmation by this method when the oral route provided faint or absent shadows.

Levene and Whitaker (38), in 1930, used the combined method with two-thirds of the oral and two-thirds of the intravenous doses and found that their patients were singularly free from any of the reactions sometimes seen following a full intravenous or a full oral dose. Such a method produced greater densities of the gall bladder shadows and permitted greater accuracy without discomfort.

In 1932, Davidson, Biguria, and Rosenthal (39) reported

on their results using the combined method in some two hundred sixty-five cases. All were ambulatory patients. Half doses of each were used. In their opinion, such a method gave accuracy comparable to that of the intravenous alone, produced a higher incidence of filling and denser shadows than the oral method, reactions were infrequent, it was time saving since no repeat examinations were necessary, and they considered it the most satisfactory means of studying ambulatory patients. However, Kirklin (36) (40) had a series of three hundred cases, shown to be non-visualized by the oral method, which he rechecked by the intravenous injection. By the latter method he could demonstrate only a one per cent greater efficiency and this convinced him that the oral method, if carefully done, was as reliable as the intravenous.

Bockus (41) reported a small series of cases in 1931 indicating that the intravenous method was superior to the oral if only one study was carried out.

### C. Modifications.

Boyden (42) (43) was the first to demonstrate that foods such as egg yolk and cream were the most efficient in emptying the gall bladder in animals. Such meals were utilized clinically in 1926 by Whitaker (44) (37) to speed up the emptying time of the gall bladder in cholecystography in humans. This procedure was generally employed clinically until 1931 when Levyn (45) introduced a modified method of administering fats by substituting a mixture of egg yolk, lecithin, glycerine, and alcohol. The lecithin was considered the active stimulant. By this method examinations were less time consuming, only a small dose was necessary, gastric peristalsis was not retarded so that the stomach emptied promptly and barium meal examination could be done sooner, it eliminated the aversion of many patients to eggs and cream, and it provided a standardized method of administering a gall bladder stimulant in lieu of the many varieties of fat meals commonly used.

Whitaker and his associates (37) (46) conducted numerous physiological experiments upon the effects of various food substances on the emptying of the gall bladder and concluded that a carbohydrate meal could be given without any effect. In 1931 Whitaker and Ellsworth (47) (48) offered an improved "double oral" method of cholecystography which was based on this physiological principle. Two full doses of the iodine salt were given--one after the regular noon meal and one after a carbohydrate evening meal the day before the films were made. By



this procedure a large amount of dye could be given at sufficient intervals to allow more time for better concentration yet the patient had nourishment. Their results gave much higher densities in the shadows produced.

Antonucci (49) shed new light on the relation of carbohydrates and cholecystography when he announced his "rapid" method in 1932. He used two to three grams of dye dissolved in 125 cc. of forty per cent glucose solution given slowly by the intravenous method. This was followed by insulin. Visualization of the gall bladder usually occurred within one-half hour. It was his opinion that the dye necessitated the presence of glucose in the liver to be absorbed and that the dye first uses the glucose from the blood stream, determining an afflux of the glycogen from the tissues if this becomes exhausted. The glycogen is then transformed into glucose which is partly utilized by the dye and partly serves to re-establish the normal glycemic level altered by the introduction of the disturbing substance. However this may be, it seems certain from the research performed so far that the glucose plays a great part in the utilization of the dye. Insulin is added so as to produce a more rapid and more complete utilization of the glucose on the part of the liver but its advantages have not been proved beyond doubt. Kestel (50) mentions the report of Zappala who reported no errors in one hundred of Antonucci's cases and he also reported that two

German workers, Biederman and Becher, obtained good shadows in two or three hours when seventy-five grams of glucose were given orally. However, Jung and Moore (51) failed to observe shadows more rapidly, or to improve the quality of the cholecystograms by the oral administration of glucose. Basing his work on the theory that adding to the glucose reserve of the body may accelerate oral cholecystography, Kestel (50) suggested the use of a carbohydrate meal instead of a fat meal. In a small series of thirty cases which showed relatively faint shadows, the patients were given the carbohydrate meal--fourteen had denser and smaller shadows in two hours, eight had same intensity but shadows were reduced in size, five varied considerably, and three disappeared. His results were not uniform but he suggested an advantage due to increased density and smaller shadow which might allow stones or other negative shadows to be discovered when overlooked in the original cholecystogram.

In 1932, Sandstrom (52) introduced the so-called fractionated oral administration. He called attention to the fact that the phthaleins, once introduced into the system, circulate for a rather long time in an enterohepatic cycle. After being eliminated through the liver and its intermediary, the bile, they are reabsorbed through the intestine, and so on. By introducing orally during each phase of the cycle additional small doses of the salt one may obtain a more com-

plete absorption. Frantionated method is entirely harmless to patient and has no damaging action on the liver.

Intensified oral cholecystography was introduced in 1934, by Stewart and Illick (53) (54). This method was suggested to them when they noted that the gall bladder shadow became more intense when starvation was continued beyond sixteen hours. The technique is based on three factors:

1. Increasing and fractionating the total dose of dye after the principle demonstrated by Sandstrom (52).
2. The free administration of sugar preceding and during the roentgen examination. This is based on the ample evidence that sugar splits up into glucose and other products and that the glucose acts as a whip for liver function including the faster and more complete absorption of the tetraiodophenolphthalein as demonstrated by Antonucci (49).
3. The use of the fast Potter-Bucky diaphragm and an exact exposure technique.

Intensified oral cholecystography requires additional work, patience and rather more time than the usual procedure, but the improved results amply compensate for these disadvantages. It is of particular value in faint shadow cases where the proper interpretation is difficult.

At the Cleveland Clinic in 1935, Collins and Root (55) began the use of pitressin in selected cases having confusing densities in the right side. Not uncommonly, more gas was noted in the intestinal tract after enemas than before. With the use of pitressin instead of enemata, they found results more effective by this simple procedure which required less time and was less troublesome to the patient.

#### D. Toxicity, Reactions, and Contraindications.

Since the introduction of tetraiodo phenolphthalein into medicine for cholecystography, attention has frequently been directed by various observers to the toxicity and the hepatic and renal lesions produced by this dye. Abel and Rowntree (4), who worked with the phthaleins as early as 1909, observed no toxic effects. Graham and Cole (1) noted toxic effects only when large doses were given intravenously. However, Ottenberg and Abramson (56) reported the production of extensive degeneration in the liver lobules after intravenous injection. Their doses were four to six times larger than the dose per kilogram of body weight necessary for cholecystography in man and they simply cautioned against the use of the dye in the presence of any liver damage. Rosenau's (57) experience was similar to that of these workers and he warned against the indiscriminate use of the dye.

Maddock and Whitaker (58) experimented in animals which had their common ducts ligated and found that the animals would tolerate seventy-five to eighty per cent of their estimated lethal dose. Graham and his associates (2) observed that many human beings with jaundice, due to common duct obstruction, had no increase in toxic symptoms following dye administration. On numerous occasions they removed small pieces of liver at operation in human subjects and never observed any evidence of hepatic damage. They also mention

Pribam, Grunenberg, and Straus, three German workers, who reported the administration of tetraiodo phenolphthalein in a case of subacute yellow atrophy of the liver without the production of any significant reaction. A good shadow of the gall bladder was obtained. Graham, Cole, Copher, and Moore considered cardiac decompensation, arteriosclerosis, and threatened uremia as the chief contraindications.

A British worker, Carmen (59), in 1926, gave an excellent description of the reactions observed following the intravenous administration of sodium tetrabromphenolphthalein. More than one-half the patients experienced systemic reactions in varying degree. In most cases the symptoms were trivial, but in ten per cent the reaction was marked and in two per cent severe. The typical severe reaction began within five or ten minutes with a sense of uneasiness, followed by pain in the dorsal and lumbar region, flushing of the skin and a rise of from ten to fifty mm. in blood pressure, followed within three to five minutes by a sharp fall. After this, patients sometimes had intestinal cramps, nausea, vomiting or incontinence of the bowel and bladder. Systemic reactions occurred especially often in cases of obstruction of the common duct, in cardiovascular disease and in persons with extremely neurotic tendencies.

Huddy (60), in 1926, reported a death following the intravenous injection of a large dose of sodium tetraiodophen-

olphthalein.

In 1927, Friedenwald, Feldman, and Kearney (61) experimented rather extensively with dogs and concluded that tetraiodo phenolphthalein administered orally for purposes of cholecystography, even in massive doses, did not produce degenerative nor necrotic changes in the liver or kidneys.

In 1928, Fitz (62) reported a reaction following intravenous injection of the dye in a case of angina pectoris. During and following the injection the clinical course was characteristic of a cardiac infarct. An uneventful recovery followed.

Dick and Wallace (63), in 1928, reported that the common symptoms following dye injection were varying degrees of upper abdominal pain, nausea, vomiting and diarrhea, often attended by a rise in temperature. Three cases were described in which they considered the dye accelerated the course of the patients' illness and contributed to their fatal endings. One case was one of common duct obstruction due to stones with associated acute pancreatitis, the second was one of jaundice with cholelithiasis, and the third case died from acute yellow atrophy of the liver thirty hours following injection. They carried out some experimental work in cats and concluded that obstruction at the ampulla of Vater might produce an acute pancreatitis following dye injection and considered it dangerous to give the dye in the presence of jaundice.

Adams (64), in 1929, reported that reactions ranged from slight disagreeable sensations to severe shock and occasional death. The common subjective phenomena were apprehension, feeling of oppression, warmth and flushing, sensation of constriction in the chest, shortness of breath, vertigo, and faintness. Objective symptoms were restlessness, flushing, and dyspnea. Three types of severe reactions were described:

1. Those associated with vasomotor collapse and shock probably related to sensitization and anaphylactic shock.
2. Those dependent on preexisting cardiovascular disease.
3. Those occurring in the presence of liver damage or an acute process along the biliary tract.

Davis (65), in 1931, described flushing, nausea, vomiting, palpitation, back pain, dizziness, sensation of warmth, abdominal pain, headaches, weakness, chills, and fever. These phenomena all belong to the collapse or shock-like group of reactions. No fatalities occurred. He considered evidence of myocardial damage and a systolic blood pressure above 180 as contraindications. In an attempt to lessen the reactions, he gave a series of patients five minims of one to one thousand adrenalin immediately before the dye injection, without any beneficial result.

One of the most extensive studies of this nature was that made by Palmer and Ferguson (66), in 1933. The following



table shows the frequency of the common reactions in two thousand, one hundred thirty-five cases:

	Per Cent
No reaction.....	42.6
Flushing.....	42.4
Nausea.....	15.7
Vomiting.....	3.2
Pain in abdomen.....	17.3
Pain in back.....	13.9
Dizziness.....	3.8
Headache.....	4.4

Almost one-half of the patients had no reactions whatever. The majority of the remainder had only slight transient disturbances, and a few had moderately severe reactions. Three serious reactions, including one death, were encountered. They considered cardiovascular lesions such as decompensation, coronary sclerosis, or angina pectoris as absolute contraindications to intravenous cholecystography.

### E. Radiographic Aspects.

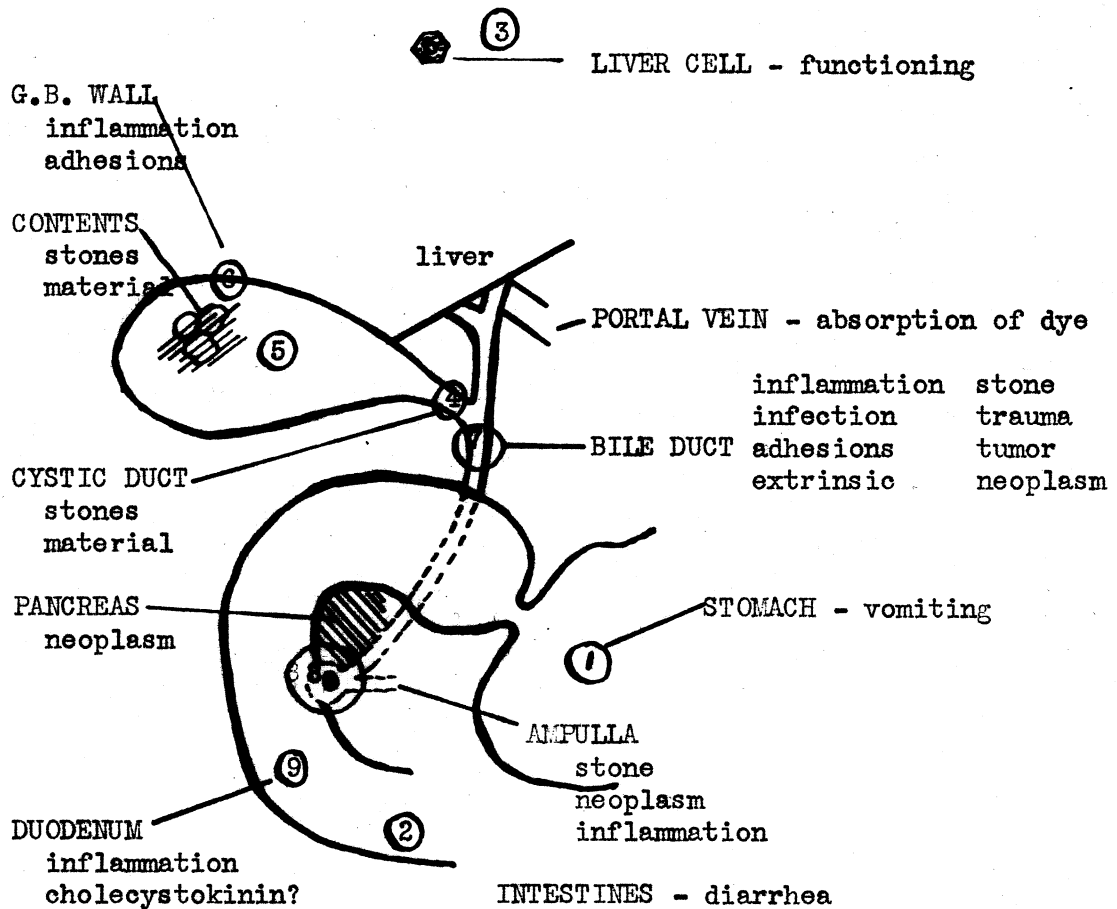
Before cholecystography was known, the necessity of an exacting technique to exhibit the gall bladder was fully appreciated. Painstaking roentgenographic technique is a prime requisite for efficient diagnosis, and this applies to all methods of cholecystography, whether the drug is given orally or intravenously. Probably in no sphere of radiology is the highest standard and most meticulous accuracy of technique more important. Many authors have emphasized this factor repeatedly but particularly Kirklin (40) and Barclay (67). Prevention of movement is a prime consideration. Certain small points are essential--the patient should lie on his face in a comfortable position, high milliamperage and a short time of exposure, the patient is immobilized with a broad canvas band drawn tightly over his back, and he is required to exhale deeply and then cease breathing during the exposure. Preliminary rehearsal is beneficial. Position of the gall bladder with regard to the patient's habitus must be considered. It is imperative that the voltage of the rays is proportioned to the thickness of the patient. A flat, Potter-Bucky diaphragm increases the clarity of the cholecystogram. Intestinal gas is combated by requiring an enema of warm soap suds on the morning of the test, and this also cleanses the bowel of fecal material.

Position of the patient is very important. Barclay (68)

pointed out the advantages of the lateral position in certain cases. In 1936, Zaldin (43) emphasized the fact that the left anterior oblique position was especially indicated in non-visualized cases in which a mesial location of the gall bladder was suspected. Again, in 1937, Feldman (69) stressed the probability of faulty roentgen technique as the principal cause of error in non-visualization or in cases in which the gall bladder was overshadowed by the hepatic flexure. He emphasized the importance of obtaining views of gall bladder in different positions and recommended the use of the left oblique or left lateral position as a routine procedure in cholecystographic study.

## V CHOLECYSTOGRAPHIC INTERPRETATION

Before discussing the interpretation of cholecystograms, it might be well to consider briefly the various possibilities affecting the roentgenographic study. The following diagram (70) affords a concise but adequate illustration of the variables to be considered.



Note: The sequence of numbers in the above diagram represent the course of the cholecystographic dye in the body.

#### A. Normal Response.

Preliminary films before the dye is given reveal no gall bladder shadow. After the tetraiodophenolphthalein the gall bladder outline becomes more intense from the twelfth to the sixteenth hour, is of normal size, shape, and position and contracts down markedly after a meal, and shows no gall stones. The gall bladder must fill with the dye, concentrate it, greatly contract after a meal, and completely empty. There must be no blurring or fuzziness of soft tissue or bony outlines from respiration or movement and bony detail in the lower ribs and vertebral bodies must be clear cut and distinct. (70)

#### B. Persistency of Shadow.

In some cases the gall bladder fails to respond to the stimulus of food and does not contract and empty as it should. This is usually fairly reliable evidence of a deficiency in the muscular tone of the gall bladder. One sees persistency of shadow as a part of a general condition of asthenia, and is often noted in cases showing marked six-hour gastric retention after barium. When the shadow disappears after food and again faintly appears thirty-six hours after administration of the dye, it usually indicates reabsorption (66), and the finding is disregarded as of no importance. (70) Hunt (71) mentioned this finding of inadequate emptying in cholesterosis. Recently, Feldman and Morrison (72) and Lipschutz (73) have

studied the matter of delayed emptying quite extensively. The latter emphasizes this particular phase of cholecystographic study as being the most important sign in the diagnosis of biliary dyskinesia.

C. Faint Shadow.

This is probably one of the most difficult conditions to evaluate properly. Standardized routine and experience are all important factors, even then technical factors may vary within wide limits, and two examinations on the same case may result in somewhat different findings. Furst and Gelber (74) consider that faint visualization could pathologically be interpreted as:

1. The gall bladder was so thickened from old chronic inflammation that the density of the shadow of the dye-laden bile is decreased.
2. That the faint shadow resulted from some interference with the normal function of concentration. This was especially true in acute exacerbations of chronic cholecystitis or in a passing edematous condition of the mucosa of the gall bladder. In the presence of an acute inflammation there is considerable edema, and that edema in the tissue decreases rather than increases absorption.
3. That the gall bladder is so packed with stones as to allow only a small amount of the opaque dye to enter.

Rehfuss (70) mentions the findings of German workers like Bronner, Schuller, Rosenthal, and Licht who believe that the inflamed membrane in acute cases absorbs the contrast bile in increased amounts and more rapidly than normal, so that by the time films are taken, the percentage of iodine in the opaque bile mixture is not sufficient to cast a shadow. There are many cases of old sclerotic gall bladders in which the function of concentration is defective, resulting in a faint shadow. There are probably many other individual causes for faint shadow but the important fact is, that regardless of whether the dye is given orally or intravenously, the finding of a faint shadow usually indicates pathology. It should always be carefully studied and correlated with the history and clinical picture with re-examination in certain cases. (70)

D. No Shadow or Nonvisualization.

What has been said for faint shadow cases applies in a measure to this group of cases. In this group, however, nearly all authors agree that gallstones are the most common cause of cystic duct obstruction. Constriction from adhesions accounts for some obstructive cases and extrinsic pressure from tumor or inflammatory masses may produce obstruction in certain cases. There are still a number of cases in which the explanation must be more or less theoretical. A number of possibilities have been offered.

1. The inflammatory process inhibits cell activity so completely that the dye is not concentrated (Chiray and Panel). (70)
2. The inflammatory process may cause breaking up of the bile-dye combination, and the toxic products interfere with the chemical union of the dye and bile (Rohdenberg). (70)
3. It is possible that some disturbed physiological action between the gall bladder and the sphincter of Oddi may prevent opaque bile from entering the gall bladder but this has never been demonstrated (Naunyn). (70)
4. Kirklin (40) claims that a meal containing fats in the evening just before taking the oral dye test results in twenty-five per cent more cases of faint or not shadow than if a fat-free meal is allowed.
5. Lahey and Jordan (75) blame the colon and state that in forty-four per cent in a series of sixty-five cases, the gall bladder filled normally after five to ten days of bowel management, whereas, with the same intravenous technique it had previously shown an absence of filling or inadequate filling.
6. Lyon and Swalm (76) point out that catarrhal ob-



struction of the cystic duct is a common occurrence and is frequently seen in grade I cholecystitis. The Graham test shows nonvisualization thus giving surgical indication for a medical condition.

7. Speaking of the limitations of cholecystography, Eusterman (31) called attention to false positives in asthenic or neurasthenic patients with gastric subacidity and lowered basal metabolic rate and also mentioned papilloma and duodenal ulcer as causes.
8. Good and Kirklin (77) reviewed the histories of seven hundred thirty-three cases at the Mayo Clinic. Included in the group were peptic ulcer, pernicious anemia, hyperthyroidism, myxedema, diabetes, obesity, pulmonary tuberculosis and chronic appendicitis. All had oral cholecystography. One hundred sixty-seven had gall bladder dysfunction. The gall bladders of one hundred six of these one hundred sixty-seven were examined at operation or necropsy--one hundred four had gall bladder disease, only two were normal. Error was only 1.9 per cent. In fifty-seven of sixty-one not operated, the clinical diagnosis corresponded with the cholecystography. In the remaining four cases the clinician

did not feel that the evidence warranted a diagnosis of cholecystic disease. They concluded that extra biliary conditions embraced in this study had little or no influence on the function of the gall bladder, as evidenced by cholecystography.

9. Hunt (71) reviewed a series of two hundred ninety-seven cases and reported that in ninety per cent of nonvisualized cases, stones were found at operation. He stated that excretion of the dye is prevented in cases showing an icteric index above twenty or with well marked clinical jaundice, rendering administration of no value in such cases, even though no untoward symptoms may occur. Furst and Gelber (74) made similar observations as well as many others. Visualization may be altered by certain physiological variations, often being faint during pregnancy due to stasis and added density, and faint in diabetes due to rapid elimination associated with the high blood sugar. Reflex emptying, supposedly from vagal stimulation, often occurs with carcinoma of the stomach and rarely with duodenal ulcer.

#### E. Deformity of Shadow.

Throughout the last five years' experience in cholecystography there have been noted with increasing frequency

deformities of the gall bladder shadow of varying nature, elongations, sacculations, folds, angulations, constrictions and the like have been observed in gall bladders which gave a normal response to the dye. For the most part they are in the nature of anomalies and not very significant. However, one must distinguish between deformities of this class and those caused by pericholecystitic adhesions. In the latter, there is usually a malposition, with or without evidence of traction. The long axis of the gall bladder is commonly directed inward, instead of downward or outward. The edges of the shadow are apt to be roughened and irregular, especially in the presence of stones. With a typical normal response to a meal the gall bladder contracts to about one-quarter of its size when distended. Such a finding rules out any dense adhesions from pericholecystitis, but a fadeaway emptying, without any evidence of contraction, is strong supporting evidence of adhesions involving the serous coat. (70)

#### F. Cholelithiasis.

There are two types of stones to be considered in relation to cholecystography, the opaque and the non-opaque. The former contain enough inorganic material, principally calcium, that they can absorb sufficient roentgen-rays to produce an image on radiography. They are sometimes called "positive", "dense" or "calcium" stones. The non-opaque stones, as the term implies, are permeable to the roentgen-rays, and are composed almost wholly of organic material,

chiefly cholesterol. They are visualized radiographically only when situated in a medium of greater or less density than themselves. They are known as "negative" or "cholesterol" calculi. These are sometimes confused with gas bubbles in the colon or duodenum and small polypoid tumors. Careful cleansing the bowel or the use of pitressin (69) usually are sufficient to eliminate the former while a detailed study of the shadow following the fat meal will aid in the differentiation of the latter.(2)

## VI DIAGNOSTIC EFFICIENCY AND EVALUATION

Statistics relative to the accuracy of cholecystography are generally based on operative findings. Because of this, the cholecystographic evidence alone is open to question. In most instances there is a positive clinical as well as positive cholecystographic evidence of biliary disease. However, Kirklin and Blake (78) summarized the cholecystographic evidence in patients not submitting to surgery but who did have a final clinical diagnosis of cholecystic disease. They found that the cholecystographic data coincided with the clinical diagnosis in approximately ninety per cent, which approaches the accuracy of cholecystography in cases proved by operation.

On the other hand, Jenkinson (79) cited a series of cholecystographic examinations done on ninety-two patients in whom all had symptoms thought to be due to gall bladder disease. Seventy or seventy-five per cent of these showed normal cholecystograms and only twenty-two pathologic responses were obtained radiographically. Eight, or forty per cent, of the patients with nonfunctioning gall bladders showed a normal response radiographically after medical management. Of the twenty pathological cases, five, or twenty-five per cent, showed a negative cholecystographic response on two or more occasions even after medical management. In his opinion, one negative cholecystographic response is not

an indication for immediate operative intervention even in the presence of gall bladder symptoms.

In 1934, Rose (80) summarized the data of twenty American authors who reported statistics concerning their series of cholecystographies, particularly those checked by surgery. These twenty authors reported a total of 39,280 cases, of which 5,983 came to operation. The largest number of cases is from the Mayo Clinic, in which 3,517 were operated on out of a total of 25,191. Kirklin divided the cases into four groups with respect to the reliability of the x-ray diagnosis:

1. Non-functioning gall bladder, with and without stones, 95 per cent.
2. Poorly functioning gall bladder, with and without stones, 94 per cent.
3. Normally functioning gall bladder, with stones, 100 per cent.
4. Normally functioning gall bladder, without stones, 81.5 per cent.

Averaging the first three figures of his conclusions, it is found that in 96 per cent of the cases the x-ray diagnosis of a pathologic gall bladder was confirmed by operation, an error of only 4 per cent, while the x-ray diagnosis of normal was found to be erroneous in 18.5 per cent.

Author	CHOLECYSTOGRAPHY				SURGICAL CHECK	
	No. of Cases	Method	Normal	Path.	Normal	Path.
					Correct Per cent	Correct Per cent
Carman	178	ivi			39	87.0
Zink	663	both			131	94.2
Stewart-Ryan	100	oral	40	60	23	95.0
Whitaker	60	ivi			28	93.0
King-Martin	407	oral			62	55 88.0
Chandler-Newell	662	both			50	
Aspray	493	both	186	312	80	93.7 100.0
Stewart-Illick	600	oral	273	327	69	97.1
Oakman	305	oral	143	162	37	97.3
Lord	100	both	19	81	100	52.6 86.4
Lockwood-Skinner	1500	oral	890	610	192	96.4
Watkins-Mills	625	oral	305	320	100	68.2 97.0
Case	2000	ivi			277	83.4 90.0
Robins-Goldberg	1014	oral	502	512	182	87.0
Kirklin	25191	both			3517	81.5 96.0
Moore	3044	both	1477	1567	416	98.7
Hawley	500	both	236	242	146	91.0
Beilin-Carlson	750	oral			150	100 98.3
Fleming	233	both			233	88.2
Littig-Lisk	800	ivi	403	397	151	
Rose	1616	both	911	801	295	64.7 96.7

The above table is taken from Rose (80). From this data, he concluded that the x-ray diagnosis of a pathologic gall bladder is dependable up to about 98 per cent. On the other hand, the diagnosis of a normal gall bladder by the x-ray is correct in an average of only 76 per cent of cases, although there is one report of 100 per cent. It is in this "x-ray normal" group that the co-operation between the clinician or surgeon and the roentgenologist is most important. The accuracy of the intravenous method over the oral method is only slightly better and so small that there is no appreciable difference.

Since Rose made his summary in 1934, numerous reports have appeared in the literature. The following table has been prepared from the recent literature of representative authors:

AUTHOR	YEAR	PLACE	NO. OF CASES	CHOLECYSTOGRAPHY (Accuracy in percentage)			
				Normal	Impaired	Non-vis	Stone
Palmer and Ferguson (81) (intravenous)	'35	Univ. of Chicago	102	---	58.3	90.0	---
Hunt (71) (oral)	'36	Univ. of Nebraska	297	60.0	97.6	99.0	99.0
Bloom (82) (oral)	'36	Michigan	---	70-80	50-75	95	100
Allen (83) (oral)	'37	Delaware	31	---	---	96.7	---
Collins (84) (oral)	'37	Cleveland Clinic	150	0.0	100	96.3	97
Hardman (85) (oral)	'37	Dublin	185	72.4	83.7	91.5	95.8
Univ. of Nebraska (oral)	'38	----	398	39.0	85.6	98.0	95.5

By way of summary, it may be said that above figures correspond rather well with those previously cited -- the average for the entire group is 91 per cent. Visualization of stones by cholecystographic methods seems to give the highest diagnostic efficiency with the no shadow group not far behind. The margin of greatest error seems to be with the group of cases showing normal cholecystograms. This is interesting inasmuch as the early writers all seemed to stress the high number of errors in the no shadow group of cases. This fact would seem to substantiate the improved methods of cholecystography.



With regard to evaluation of cholecystographic findings Collins and Root (84) summarized one hundred fifty cases having cholecystectomies in which the cholecystograms were accurate in 93 per cent. They concluded:

1. A gall bladder normally visualized by cholecystography may be pathologic, even though in most instances it denotes a normal gall bladder. Convincing clinical evidence is necessary in order to justify surgery on the grounds of biliary disease if the cholecystographic findings are normal.
2. On the other hand, gall bladders which are full of the calcium-type stones commonly function normally with the dye test. In the absence of stones, the routine use of multiple doses of dye should logically increase the error in diagnosis so far as normally functioning gall bladders by cholecystography alone are concerned. There must be many patients who have symptoms due to chronic cholecystitis without stones who have normal cholecystograms. The patient should not be told that his gall bladder is normal on the basis of cholecystographic findings alone.
3. Nonvisualization of the gall bladder without evidence of opaque calculi usually indicates a non-functioning gall bladder containing calculi of the

cholesterin type, often blocking the cystic duct. But consideration should be given to the possibility of other causes and re-examination done in certain cases.

The author of this paper has made a statistical study of 836 cases of biliary disease in the University of Nebraska Hospital from July, 1925 through July, 1937. In this group, there were 408 cases having cholecystographic studies who were submitted to surgery. A tabulation of the cholecystographic findings correlated with the pathological findings will be found on the following page. It might be well to keep in mind that all cases over this eleven-year period are included in the summary. This means that the cholecystographic methods used in these cases have not been well standardized inasmuch as the technique used has advanced in relation to the improved methods in cholecystography. However, the oral method has been used in the majority of cases and the usual routine consisted of:

1. Two doses of dye on successive days following the evening meal.
2. Butter, cream, and greasy foods were forbidden.
3. Rectal enema on third morning.
4. Eight cc. paregoric following second dose.
5. Re-examination in cases not showing dense shadow or calculi.  $\frac{1}{2}$  glass 20 per cent cream given directly following recognition of a dense shadow.

## Correlation of cholecystography with pathology found in 408 cases:

CHOLECYSTOGRAPHIC FINDINGS	NO.	PATHOLOGICAL FINDINGS	NO.	PER CENT OF ERROR
1. Normal response	18	Negative gallbladder	7	61.0
		Cholecystitis with stone	1	
		Cholecystitis no stone	8	
		Cholesterosis no stone	2	
2. Non-visualized with no evidence of stone	153	Cholecystitis with stone	110	4.0
		Cholecystitis no stone	25	
		Cholesterosis with stone	3	
		Acute Cholecystitis, stone	3	
		Carcinoma of Gallbladder	5	
		Carcinoma of Pancreas	1	
		Negative gallbladder	6	
3. Non-visualized with opaque stone seen	28	Cholecystitis with stone	26	7.0
		Cholecystitis no stone	1	
		Carcinoma of Gallbladder (no stone)	1	
4. Stone with impaired concentration	80	Cholecystitis with stone	70	8.8
		Cholecystitis no stone	2	
		Cholesterosis with stone	3	
		Cholesterosis no stone	1	
		Negative gallbladder	4	
5. Stone with normal concentration	4	Cholecystitis with stone	4	0.0
6. Impaired concentration with normal emptying	125	Cholecystitis with stone	35	14.4
		Cholecystitis no stone	48	
		Cholesterosis with stone	4	
		Cholesterosis no stone	20	
		Carcinoma of Pancreas	1	
		Negative gallbladder	17	

## Summary:

- (1) 82 per cent of the non-visualized group contained stones.
- (2) 40 per cent of calculi were visualized by cholecystography.
- (3) 8 per cent error in cholecystographic diagnosis of stones.
- (4) 11 per cent gross error in cholecystographic diagnosis.
  - (a) 61 per cent with normal response were pathologic (11 of 18)
  - (b) 7 per cent histologically normal gave dysfunction (27 of 381)
- (5) 87.5 per cent non-visualization in biliary tract carcinomas (7 of 8).

#### Discussion:

In the non-visualized group of cases there were 149 of 181, or 82 per cent, which had stones discovered at operation. This figure compares favorably with the 78 per cent reported by Collins (84) in a series of 100 cases. It is interesting to note that seven of eight, or 87.5 per cent, of biliary tract malignancies failed to produce a gall bladder shadow. On the other hand, there were six in this group giving no shadow and that were found to be negative in the pathologist's report. Checking this group, there were associated extra biliary conditions in all--two with diagnosis of neurasthenia, two with peptic ulcer, one toxic thyroid, and one with nephrolithiasis. The latter four were all diagnosed at operation. Thus, nonvisualization does not necessarily indicate a pathologic gall bladder and this diagnosis should not be made unless there is a suggestive history, and all other causes for the symptoms have been excluded by a complete examination.

Forty per cent of calculi, or in 103 of 265, were visualized by cholecystography. The error of 8 per cent in cholecystographic diagnosis of stones may be attributed for the most to confusing densities on the right side due to gas in the intestine in spite of the enemata that were given.

There was 11 per cent gross error in cholecystographic diagnosis. On the negative side were eleven cases having normal cholecystographic findings in which there was found micro-

scopical evidence of pathology. It will be noted that four of the cases showing normal concentration revealed the presence of stones which was confirmed at operation and the pathologist reported chronic cholecystitis. Of the eleven under consideration, one was found to contain stones so it is possible that pathologic gall bladders containing stones, function with the cholecystographic dye. Collins (86) considers this a common occurrence. It should be remembered that this represents only eleven of 408 cases so that relatively speaking, this percentage of error is more apparent than real.

On the positive side only 7 per cent, or 27 of 381, having impaired cholecystographic response, were found to be histologically negative. The associated pathology found in this group included pericholecystic adhesions in three, one peptic ulcer, one ptosis of colon, one fatty degeneration of liver, and one with a gastric neoplasm. In addition, it may be said that there is no universal agreement among pathologists as to what constitutes a pathological gall bladder. Inasmuch as there was an incidence of 7.2 per cent, 47 of 570 operated cases, of histologically negative gall bladders in this series under consideration, it can be safely said that the pathologists were rather critical in their reports. Even so, this margin of error is so small that it nearly nullifies the error on the negative side.

The diagnosis of cholesterosis by cholecystographic

methods is uncertain at best. Two gave normal response, three with associated stones were non-visualized, and the majority showed impaired concentration or faint shadow. In many instances, it was observed that although there was fairly good concentration of the dye there was delayed emptying in this group of cases.

## VII CHOLECYSTOGRAPHY AND PROGNOSIS

In the literature to date, there has appeared only one article relative to prognosis in cholecystography. This was written by Graham and Mackey (87). They summarized the clinical results in 114 cases of stoneless gall bladder subjected to cholecystography as follows:

CHOLECYSTOGRAPHY	CLINICAL RESULT					Per cent Relieved
	Total	Well	Improved	Unimproved	Death	
Normal	10	5	1	4	0	60
Deformed shadow	8	4	2	2	0	75
Faint shadow	75	22	22	28	3	59
No shadow	<u>21</u>	<u>6</u>	<u>7</u>	<u>5</u>	<u>3</u>	<u>62</u>
Total	114	37	32	39	6	60

The ten patients who were operated on, in spite of a normal cholecystographic response, had their operations because it was felt that the symptoms warranted the operation in spite of the negative roentgen examination. And of the six patients considering themselves either well or improved after operation, Graham is of the opinion that probably the removal of the gall bladder had little or nothing to do with the relief of the symptoms. Routinely, he removed the appendix and is of the opinion that possibly the removal of appendix was responsible for the relief of the symptoms.

The gall bladder appearing normal on cholecystographic examination rarely shows any marked pathological change in their opinion. The fact that only 62 per cent of non-visualized cases were relieved of symptoms caused astonishment, but they

suggested the possibility of extra biliary conditions as causes in the unimproved cases. They concluded that in the absence of severe pain, the beneficial results to be obtained by cholecystectomy in cases of a stoneless gall bladder are likely to be unsatisfactory in 40 per cent and to subject patients with beginning cholecystic disease is not always the best judgment.

A comparable study was made in the University of Nebraska series compiled by the author. There were 229 patients having Graham-Cole studies subjected to operation in whom follow-up records were obtainable. Patients having cholelithiasis were also considered. The results are summarized briefly in the following table:

CHOLECYSTOGRAPHY	CLINICAL RESULT					Per cent Relieved
	Total	Well	Improved	Unimproved	Death	
Normal	11	8	2	1	0	91
Faint shadow	56	33	9	9	5	76
No shadow	77	51	16	3	7	87
Stones	85	61	16	3	5	92
Total	229	153	43	16	17	85

The fact that 91 per cent of the cases showing normal responses to the Graham test considered themselves well or improved needs further explanation. There were only eleven cases in all and only two of the eleven had histologically negative gall bladders. Six had mild cholecystitis, two had cholesterosis, and one had cholecystitis with cholelithiasis. Statistics indicate that in a stone case one may expect 90 per cent re-



lieved. Routine appendectomies were done and as Graham and Mackey (87) pointed out, the removal of the appendices could very likely account for the improvement following cholecystectomy. The single unimproved case was one of cholesterosis while the two showing only partial relief from symptoms had minimal pathology. It would seem that the ordeal of surgery might account for a certain amount of improvement in functional cases. It must be remembered that this series covers a period of ten years and it is entirely probable that some of the early cholecystograms were not so reliable.

The faint shadow group gave the poorest clinical results which compares favorably with Graham's figure. Since we have already demonstrated that 82 per cent of non-visualized gall bladders contain stones it is to be expected that the results in this group would be close to the result in the stone cases. The small difference could easily be accounted for by the extra biliary conditions which sometimes produce non-visualization. It is only reasonable to assume that stones indicate advanced pathology and we should expect a more favorable prognosis in this group of cases. However, due to the unusually high figure in all groups it can only be concluded that as a prognostic instrument cholecystography is somewhat unreliable--the figures speak more for the benefits of cholecystectomy in biliary disease.

## VIII CONCLUSIONS

1. Cholecystography is essentially a test of functional capacity.
2. The modified oral methods are comparable to the intravenous methods in efficiency and are safer and simpler.
3. Success of the methods depends upon the most careful attention to detail in preparation and radiographic technique.
4. Cholecystography in the presence of cardiovascular disease, extensive liver damage, and threatened uremia is contraindicated.
5. Composite statistics indicate a diagnostic efficiency in 90 per cent or more of cases whether the gall bladder is normal or pathological.
6. The fact that there may be error in 10 per cent of cases is good reason for not considering the Graham-Cole as an independent diagnostic instrument but should be considered together with the history and clinical picture.
7. Prognosis by cholecystography is not dependable.

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